Papers of the Week

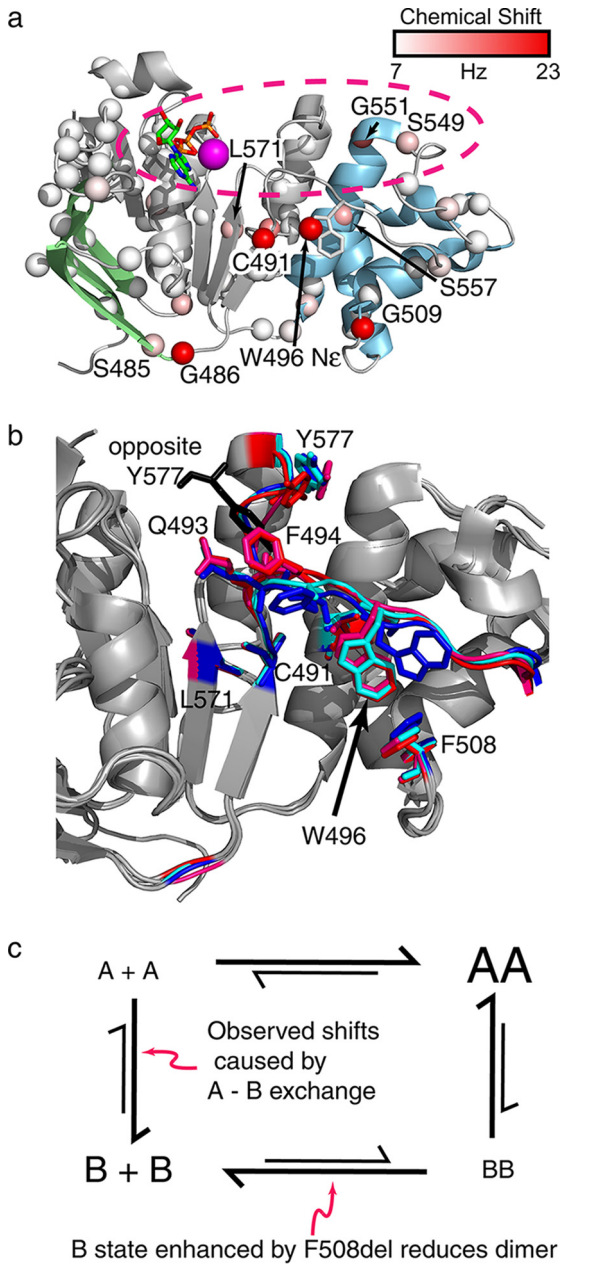
Deletion of Phenylalanine 508 in the Cystic Fibrosis Transmembrane Conductance Regulator Reduces Dimerization ◆

◆ See referenced article, *J. Biol. Chem.* 2015, **290,** 22862–22878

Deletion of Phenylalanine 508 in the First Nucleotide-binding Domain of the Cystic Fibrosis Transmembrane Conductance Regulator Increases Conformational Exchange and Inhibits Dimerization

A mutation known to occur in cystic fibrosis is the deletion of phenylalanine 508 (F508del) in the cystic fibrosis transmembrane conductance regulator (CFTR). The amino acid is in the first nucleotide-binding domain (NBD) of CFTR. This mutation leads to defective channel processing and gating problems. In this Paper of the Week, a team led by Julie Forman-Kay at the Hospital for Sick Children in Canada used nuclear magnetic resonance spectroscopy to understand how F508del affects the stability of CFTR. By studying the motions of the mutated domain, the investigators found that the mutation hinders NBD dimer formation. Forman-Kay and colleagues concluded, based on NMR spectra of various mutants and published crystal structures, that the NBD dimer interface and the Phe-508 position are linked allosterically and that deletion of Phe-508 forces the first NBD into a conformation that inhibits dimerization. The lack of dimerization reduces channel production and function. The authors say, "These results provide a potential mechanism for inhibition of channel opening by F508del and support the dimer interface as a target for cystic fibrosis therapeutics."

DOI 10.1074/jbc.P115.641134



Dimerization of the nucleotide binding domain helps stabilize CFTR.